MR VOLUMETRIC STUDY OF CEREBELLUM RELATED TO AGE AND SEX

BY

DR WAN AIREENE BINTI WAN AHMED

DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENT FOR THE DEGREE OF MASTER OF MEDICINE (RADIOLOGY)

UNIVERSITI SAINS MALAYSIA

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Supervisor:

DR WIN MAR@SALMAH JALALUDDIN

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In the Name of Allah, the Most Merciful, the Most Compassionate all praise be to Allah, the Lord of the worlds; and prayers and peace be upon Mohamed His servant and messenger. First and foremost, I must acknowledge my limitless thanks and gratitude to Allah, the Ever-Magnificent; the Ever-Thankful, for His help and bless. I am totally sure that this work would have never become truth, without His guidance.

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as I wanted. It was under their watchful eye that I gained so much drive and an ability to tackle challenges head on.

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ABBREVIATION

CSF	Cerebrospinal Fluid
CV	Cerebellar Volume
DICOM	Digital Imaging and Communications in Medicine
FLAIR	Fluid-attenuated Inversion Recovery
HUSM	Hospital Universiti Sains Malaysia
ICV	Intracranial volume
IR	Inversion Recovery
MR	Magnetic Resonance
MRI	Magnetic Resonance Imaging
NCV	Normalized Cerebellar Volume
OCV	Original Cerebellar Volume
PACS	Picture Archiving and Communications System
PD	Parkinson's Disease
SD	Standard deviation
SPGR	Spoiled Gradient Recalled
SPSS	Statistical Package for the Social Sciences, later Statistical Product and Service Solutions
TICV	Total Intracranial Volume
TCV	Total Cerebellar Volume
T1WI	T1-weighted image(s)
T2WI	T2-weighted image(s)

ABSTRAK

ABSTRAK

Tajuk:

Pengukuran Isipadu Cerebellum Menggunakan Pengimejan MR Yang Berkaitan Dengan Umur Dan Jantina.

Pendahuluan:

Perkembangan teknologi pengimejan MRI telah membuka peluang kepada banyak kajian neuroanatomi berkenaan perkembangan normal dan pengecilan struktur otak. Terdapat banyak penyakit saraf and jiwa yang berupaya merubah isipadu cerebellum, terutama penyakit sawan, penyakit Parkinson's, penyakit nyanyuk Alzheimer's, kemurungan, autism dan sebagainya. Kajian terhadap kesan penuaan terhadap cerebellum adalah penting terutama dalam proses penuaan normal dan perbandingan dengan patofisiologi penyakit kronik otak. Kajian terhadap perbezaan jantina dalam isipadu cerebellum juga telah dilihat di dalam kajian lain.

Kenyataan Masalah:

Buat masa sekarang, tidak terdapat data mengenai ukuran isipadu cerebellum untuk populasi Malaysia.

Objektif:

Tujuan kajian ini adalah untuk menentukan ukuran isipadu cerebellum berkaitan dengan umur dan jantina.

Tatacara:

Ini adalah kajian observasi keratan lintang melibatkan 164 subjek yang menjalani MRI di bawah kajian lepas. Umur subjek adalah antara 7 hingga 77 tahun. MRI telah dilakukan menggunakan pengimbas Tesla Signa Horison LX 1.0 oleh General Electric. Imej-imej MRI telah diperolehi dalam siri sagittal T1 dengan ketebalan 5 milimeter dengan 2 milimeter sengkangan. Cerebellum diukur menggunakan kaedah volumetri secara manual dikesan secara selang-seli. Jumlah isipadu cerebellum dikira dan dianalisis dengan menggunakan perisian IBM SPSS versi 20. Sempadan anatomi bagi volumetry cerebellum dilakukan dengan mengesan secara manual. Normalisasi jumlah cerebellum dengan jumlah isipadu otak telah dilakukan dengan menggunakan kaedah-kaedah bersama varians yang diperkenalkan oleh Jack *et al*. (1989). Mengesan secara manual yang menggunakan kaedah alternatif slice telah digunakan dalam mendapatkan jumlah isipadu otak seperti yang dinyatakan oleh Eritaia *et al*.(2000). Paparan imej dan manual mengesan cerebellum dan otak telah dijalankan menggunakan perisian Osirix ver.3.7.1 (Pixmeo Sarl). Data disusun dan dianalisis menggunakan statistik PASW ver.18 (SPSS Inc).

Keputusan:

Jumlah min keseluruhan cerebellum adalah 181.1 ± 24.8 cm^3. Jumlah normalisasi cerebellum telah ditayangkan untuk tidak mengurangkan perbezaan jantina jumlah cerebellum. Apabila dianalisis secara berasingan antara jantina, ujian t-bebas adalah seperti yang ditunjukkan dengan nilai p = 0.035 adalah 95% pasti jumlah isipadu normalisasi cerebellum lelaki (185.3 ± 24.1) adalah jauh lebih tinggi berbanding perempuan (177.2 ± 25.0). Menggunakan analisis

korelasi Pearson, terdapat hubungan linear yang signifikan antara jumlah normalisasi cerbellum ($p < 0.001$). Diperhatikan pekali korelasi, r adalah-0.492, yang dicadangkan terdapat hubungan negatif yang signifikan secara statistik antara umur dengan jumlah keseluruhan cerebellum di mana yang lebih tua umur, lebih kecil jumlah keseluruhan otak kecil dengan sederhana dan korelasi yang baik.

Kesimpulan:

Hasil kajian kami sediakan data normatif cerebellum dalam format asal dan normalisasi penduduk Kelantan bagi rujukan berharga dalam banyak keadaan fisiologi dan patologi penduduk kami. Data normatif adalah setanding dengan lain-lain data yang diterbitkan.

ABSTRACT

ABSTRACT

Topic:

MR VOLUMETRIC STUDY OF CEREBELLUM RELATED TO AGE AND SEX.

Introduction:

The advancement of MRI techniques has open up many neuroanatomical studies of normal brain growth and atrophy. Numerous neurological and neuropsychiatric disorders, which can cause changes in cerebellum volumes have been identified particularly epilepsy, schizophrenia, Alzheimer's dementia, depression and autism among others. Investigations of aging effects on the cerebellum are important, not only to understand normal aging process, but also for comparative study of the pathophysiology of degenerative brain disorders. Sex differences in gross cerebellar neuroanatomy have been observed in several studies. Currently there is no normative data of MR cerebellum volumetry available for Malaysian population.

Objectives:

The general objective for this study is to determine the age and sex difference of the volume of cerebellum in healthy volunteers.

Methods and materials:

This was a cross sectional study involving 164 subjects who underwent MRI. The age of the subjects ranged from 7 to 77 years old. MRI was performed using Signa Horison LX 1.0 Tesla scanner by General Electric. MRI images were obtained in T1 sagittal sections with 5milimeter thickness with 2-millimeter

gap. Cerebellum volumes were measured using manually traced slice volumetry method. The mean (SD) of total cerebellum volume was calculated and analyzed using IBM SPSS version 20.

Anatomical boundaries for cerebellum volumetry done with manual tracing. Normalization of cerebellum volume with intracranial volume was done by using co-variance methods introduced by Jack *et al*. (1989). Manual tracing using alternate slice method was utilized in obtaining intracranial volume as described by Eritaia *et al. (2000)*. Image display and manual tracing of the cerebellum and intracranial areas were performed using Osirix software ver.3.7.1 (Pixmeo Sarl). Data was compiled and analyzed using PASW Statistic ver.18 (SPSS Inc.).

Results:

The overall mean normalized cerebellar volume is 181.1 ± 24.8 cm^3. When analyzed separately among gender, normalized cerebellar volume was significantly higher in male (*p* value= 0.035; 95% +- CI). There is a statistically significant negative correlation between age and total cerebellum volume (*r* is -0.492). Cerebellar volume becomes smaller at older age with moderate to good correlation.

Conclusion:

The study provided a reference data of cerebellar volumes in original and normalized formats for normal Kelantan population for a valuable reference in many physiological and pathological conditions for local population. The mean normalized cerebellar volume was statistically significant in genders with larger

volumes in male subjects. They also had larger intracranial volumes than female. There is significant relationship between normalized cerebellum volume with age.

INTRODUCTION

SECTION 1

INTRODUCTION

Brain size and volume is one of the useful parameters describing functional characters of the body. Many methods of morphometric studies in recent advancement of CT and MRI of the brain have given the previous researchers new insights in the field of wide range of neuroanatomy and neuropsychiatric diseases.

Aging of the human brain is a differential process in which significant deterioration in some regions coexists with relative preservation in others. Although this pattern is well apparent in the cerebral cortex, it is however unclear whether it can be extended to the structures of the posterior fossa particularly cerebellum (Raz *et al.*, 1998).

Cerebellum is a region of the brain that plays an important role in coordination of voluntary movement, gait, posture, speech and motor functions. It is also involved in some cognitive functions such as attention and language, and in some emotional functions such as regulating fear and pleasure responses. Therefore, cerebellar volume quantification is important to aid the understanding of its development in relation with many variability such as age and gender.

Gender and age-related volumetric differences in cerebellum anatomy has been an interesting subject for researchers. There are many studies in the

literature where anatomical structures in brain including cerebellum are measured quantitatively in terms of volume, area, width and length. Investigations of aging effects on the cerebellum are important, not only to understand normal aging, but also for comparative study of the pathophysiology of degenerative brain disorders.

Many neuroanatomical studies of normal cerebellum growth and atrophy have been reported since the development of MRI. Sex differences in cerebellar shrinkage with aging have been suggested result from intrinsic or extrinsic factors such as hormones and hypertension. Interactions with environmental factors, such as acquired disease, exposure to toxins, and trauma, also can lead to developmental deviations and can also result in loss of cerebellar tissue.

The studies of previous investigators on the changes of cerebellum size according to age showed controversial results. Some studies suggested the decrease of cerebellum size with aging while other studies reported no significant decrease. The effect of gender is also arguable. Moderate shrinkage of the cerebellum hemispheres also has been noted in post-mortem studies and in some in vivo investigations.

MRI studies have correlated cerebellum morphology with symptomatology in several disorders, including schizophrenia, Parkinson disease, Wilson disease, Alzheimer's disease and autism suggesting that morphometric data may indirectly reflect underlying neurochemical or pathologic process. Coffman *et al.* (1990) found no differences between schizophrenics

and controls, whereas Nasrallah *et al.* (1982) reported that schizophrenics have larger cerebellum structures than controls.

To this date, studies reporting the total cerebellar volume and total intracranial volume are limited especially in the context local population. To our knowledge, no study has been carried out to characterize the gender differences, and effects of age on cerebellum in Malaysia. Our study aims is to find out the normalized volumes of cerebellum and to evaluate their relations with sex and age in healthy subjects.

LITERATURE REVIEW

SECTION 2

LITERATURE REVIEW

2.1 Anatomy

The cerebellum, from the Latin meaning little brain, is the largest part of the hindbrain occupying most of the posterior fossa. In the adult human brain, the cerebellum volume is about 170 cm3, weighing 160 grams (10% total brain weight). However, its surface area is 40% of the cerebral cortex, containing half the total number of intracerebral neurons.

The superior aspect of cerebellum is separated from the overlying occipital lobes of the cerebrum by tentorium cerebelli, a transverse fold of the dura mater that stretches horizontally. The posterior, inferior, and lateral surfaces of the hemispheres lie adjacent to the meninges overlying the occipital bone (Figure 2.1). The precentral fissure separates the anterior paravermian aspect of each hemisphere from the posterior aspect of the pons and junction of the pons and midbrain (Figure 2.2)(Press *et al.*, 1989).

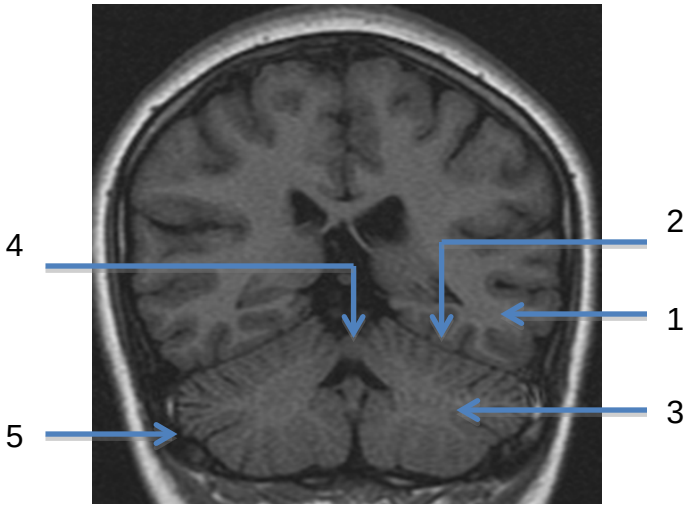

Figure 2.1 MRI image axial cut at level of cerebellar vermis

1. Occipital lobe; 2. Tentorium cerebelli; 3. Cerebellar hemisphere; 4. Vermis; 5. Occipital bone. Adapted from (Press *et al.*, 1989)

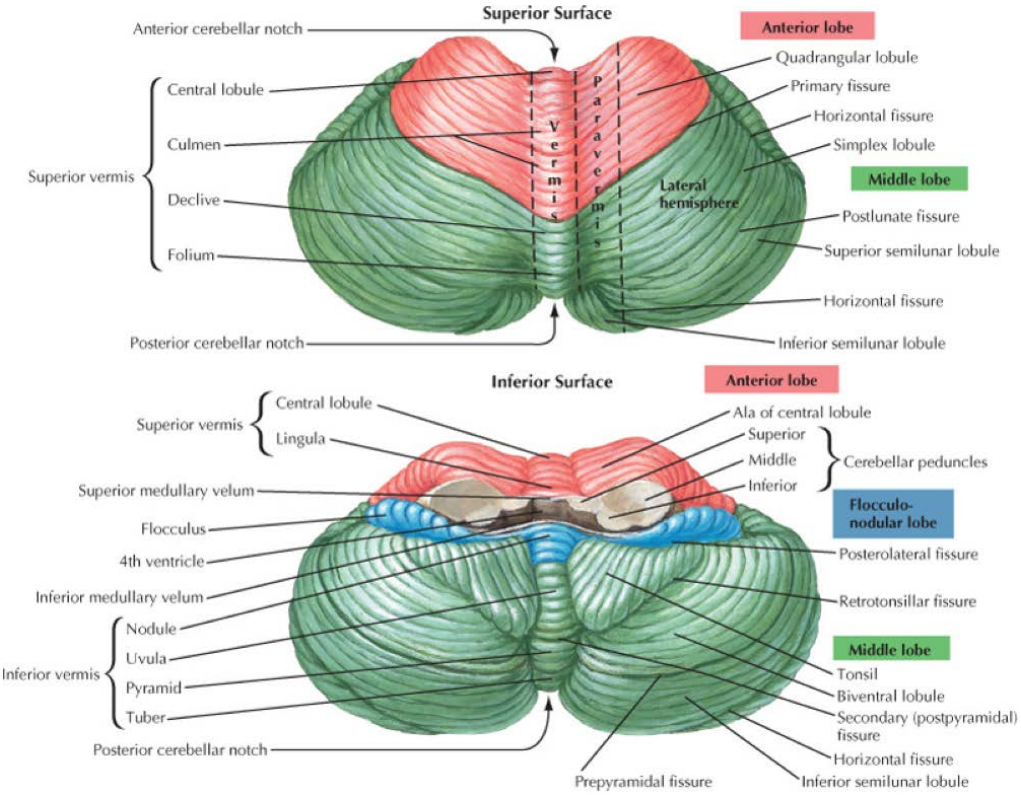

Figure 2.2 Sketches of superior and inferior surface of cerebellum.

Adapted from (Felten and Józefowicz, 2003)

The cerebellum (Figure 2.2) consists of two large hemispheres situated contiguously with the midline vermis (from the Latin, meaning worm) by paired shallow surface indentations, the paravermian sulci (Press *et al.*, 1989). The vermis is a wedge-shaped structure presenting a superior and an inferior surface separated by the horizontal fissure, the most conspicuous of the cerebellar fissures. The superior surface of the cerebellum is flattened, showing no deep grooves in the paravermian regions as the superior vermis is directly continuous with the cerebellar hemispheres on each side. Anteriorly, the superior vermis continues beyond the free margin of the tentorium cerebelli. Superiorly, it is bound by a wide, shallow, anterior cerebellar notch. The posterior inferior surface of the cerebellum is convex and lies in the occipital region. The inferior vermis is separated from the paramedian region of the cerebellar hemisphere by deep sulci. Posteriorly and inferiorly a narrow median fossa, the vallecula cerebelli, separates the hemispheres and contains the falx cerebelli (Figure 2.1 and Figure 2.2).

The cerebellum is connected with the three rostrocaudal portions of the brainstem by three paired cerebellar peduncles, superior, middle and inferior. (Figure 2.3).

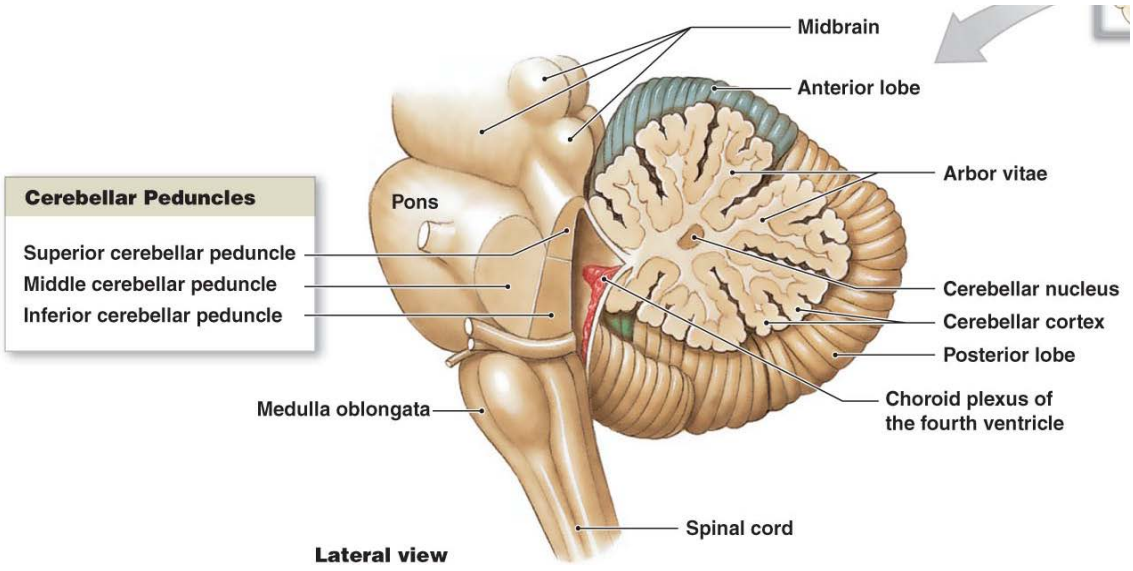

Figure 2.3 Sagittal section through vermis showing internal organization of cerebellum and the locations of the three cerebellar peduncles.

(Source: www.highlands.edu)

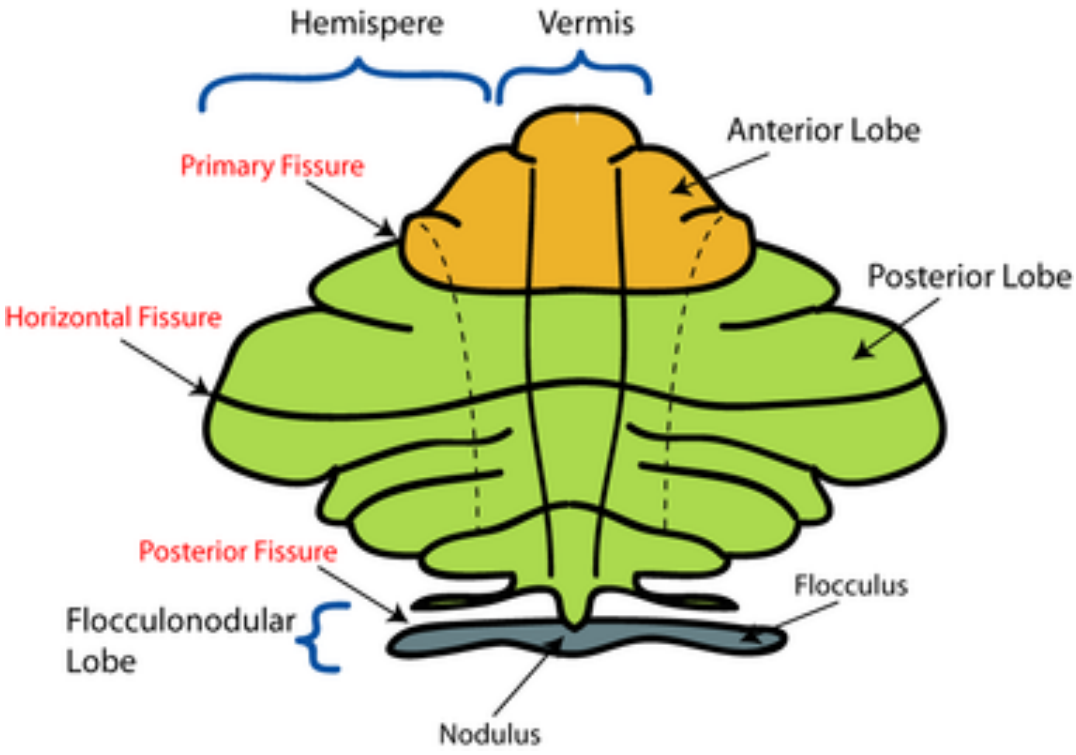

Figure 2.4 Schematic representation of the major anatomical subdivisions of the cerebellum. Superior view of an "unrolled" cerebellum, placing the vermis in one plane.

(source: wikipedia.org)

The deep primary and posterior (posterolateral) fissures extend outward from the vermis into the cerebellum hemispheres dividing them also into three portions: the anterior and posterior lobes and the hemispheric component of the flocculonodular lobe, the flocculus (Figure 2.4). Additional, shallower fissures subdivide the anterior and posterior lobes of the hemispheres into a series of lobules. The preculminate fissure separates the central lobule from the anterior quadrangular lobule (Figure 2.5).

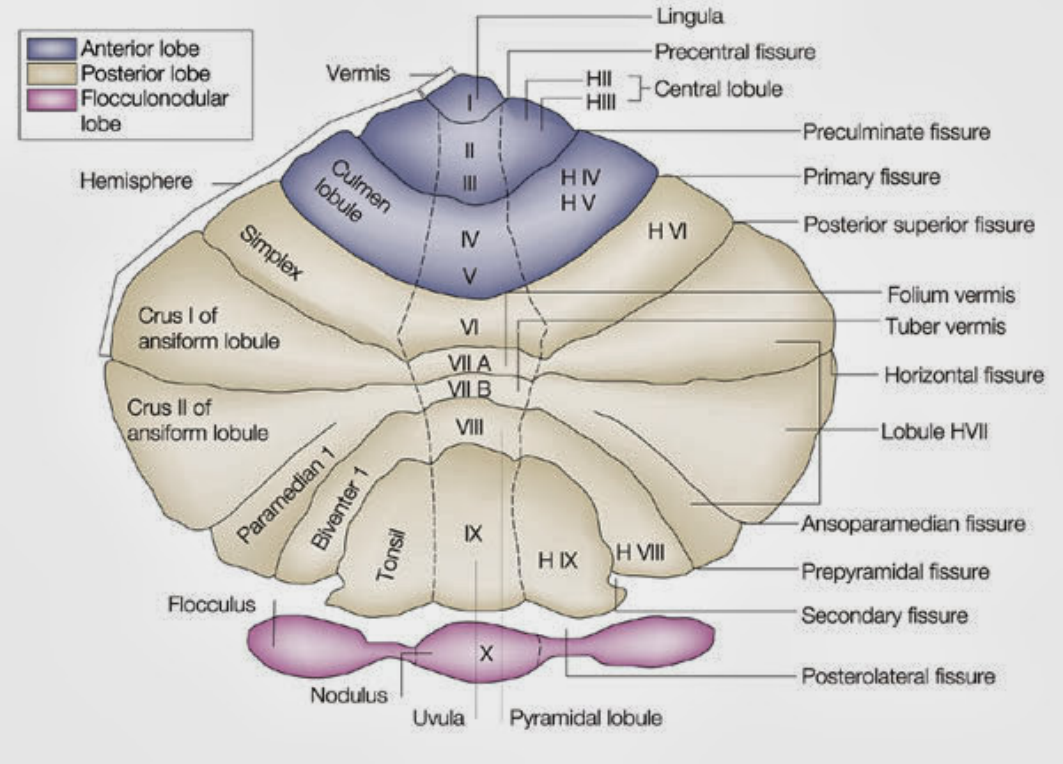

Figure 2.5 Diagram of lobar and lobular structures of cerebellum.
(Source: http://www.ehealthideas.com)

The lobules of the posterior lobe of the cerebellum are bounded by the primary fissure (which separates them from the anterior lobe) and the posterolateral fissure (which separates them from the flocculus). Three

additional fissures within the vermis extend also into the hemispheres to separate several of the five lobules of the posterior lobe of the hemisphere from one another: the superior posterior fissure separates the posterior quadrangular lobule from the superior semilunar lobule, the horizontal fissure separates the superior semilunar lobule from its inferior component and the secondary fissure separates the biventer and tonsil. Two remaining fissures are present within the hemispheres only and subdivide the remainder of the lobules of the posterior lobe: the inferior posterior fissure separates the inferior semilunar lobule and gracile lobule and the inferior anterior fissure separates the gracile lobule and biventer (Figure 2.5). The flocculus is a separate lobe of the cerebellar hemisphere and contains only one lobule. It represents the hemispheric component of the flocculonodular lobe of the cerebellum and is bounded posteriorly by the posterolateral fissure and anteriorly by the cerebellopontine angle cistern.

2.2 Function

The cerebellum is a complex structure, containing more than 50% of all neurons in the brain. It is organized in a different manner than the cerebrum (Voogd, 2003; Kandel, 2013). It is a region of the brain that functions largely outside of the realm of conscious awareness. Its best-known functions are involved in coordinating motor activities and learning new motor skills. It is particularly involved in adjusting activities to meet new conditions. However, in addition to these well-known functions, there is a growing awareness that cerebellar systems may be involved in other types of learning and also in emotional reactivity.

Recently, research has emphasized the role the cerebellum is likely to play in cognitive processing, next to its well-studied contributions to motor skills (Schmahmann, 2010; Stoodley and Stein, 2011). Clinical and basic research indicates that the cerebellum (particularly the posterior lobe of the hemispheres and vermis) regulates, integrates, and coordinates a wide variety of additional, non-motor concerns including level of consciousness, learning, memory, and motivated behavior. For example, early investigators recognized that cerebellum damage occurring in adulthood may be associated with lethargy and coma or psychosis. Others observed that retarded intellectual functioning is typically associated with developmental disorders of the cerebellum ranging from hypoplasia to near total agenesis.

Such clinical data and experimental observations require a reassessment of the role of the cerebellum in normal CNS functioning. Indeed, one investigator has proposed that the role of the cerebellum may extend far beyond regulation of simple motor activities to encompass global coordination of many additional types of behavior for the purpose of optimizing information acquisition (sensory reception) during active exploration of the environment (Bower J, personal communication). MR will likely facilitate defining the bounds of the "expanding" role of the cerebellum by providing improved in vivo identification, localization, and quantification of cerebellar disease in patients whose clinical deficits can be thoroughly (Press *et al.*, 1989)

2.3 Cerebellar Volume in Normal Aging Process

Post-mortem and in vivo imaging studies have shown that the human brain shrinks with age. The incident of volume loss varies greatly among different brain regions (Raz, 1996; Haug, 1997). The cerebellum seems to be affected by age (Ellis, 1920; Sullivan MP, 1995), although its volume loss is less as compared to the cerebrum. In some subject samples age effects on the cerebellum were insignificant (Hayakawa, 1989; Escalona *et al.*, 1991). Inside the cerebellum, some regions seem to be more prone to age-related decrease than others. Histology and computerized tomography studies reported pronounced volume loss in the anterior vermis (Koller, 1981). In magnetic resonance imaging (MRI) studies, predominant shrinkage was observed in the posterior vermis (Shah *et al.*, 1991; Raz, 1996). The hemispheres also showed shrinkage with age (Raz *et al.*, 1998).

Most structural magnetic resonance (MR) imaging studies with large sample sizes have focused on the cerebrum only or the entire brain (Good *et al.*, 2001; DeCarli *et al.*, 2005; Ikram *et al.*, 2008). Whereas studies that specifically assessed the cerebellum showed inconsistent results. Some studies reported that cerebellum volume remains relatively stable with aging (Rhyu *et al.*, 1999a; Bergfield *et al.*, 2010) whereas others found strong effects of age on cerebellar atrophy (Jernigan *et al.*, 2001; Raz *et al.*, 2001; Walhovd *et al.*, 2005; Raji *et al.*, 2009; Raz *et al.*, 2010). A histological study of the cerebellum showed that smaller weight and volume were found, and fewer neurons were counted in the cerebellum of older persons than in those of younger persons

(Andersen *et al.*, 2003). Drawbacks of this previous work are the relatively small sample sizes and use of preselected populations.

Regional volume loss does not only occur in physiological ageing. Various hereditary and non-hereditary disorders produce distinct patterns of atrophy in cerebellum and brainstem (Escourolle *et al.*, 1982). Precise quantification of brain volumes using modern imaging techniques may reveal patterns of volume loss with specificity for certain conditions related to age or disease. These patterns may be used for formulating wide range of differential diagnosis (Schulz *et al.*, 1999).

Considering the recent advances in the knowledge of functional as well as morphological compartmentalization of the cerebellum, Luft *et al.* (1997a) reported that a precise characterization of the regional patterns of cerebellar age-related atrophy is necessary.

2.4 Gender Effect on Cerebellar Volume.

Several investigators have observed sex differences in gross cerebellum neuroanatomy. Male were shown to have larger cerebellum than those of age-matched female. Although in these reports the possibility that these differences could have reflected sexual dimorphism of body size (Raz N *et al.*, 1992). In some samples, also in comparison to women, men had larger cerebellar hemispheres, cerebellar vermis, anterior vermis, and ventral pons. However, the differences do not always favor men. In one sample, women evidenced greater volume of medial cerebellar hemispheres. One report suggested that

women might show steeper age-related decline in the area of the vermis than do their male counterparts. (Escalona *et al.*, 1991)

Naftali Raz *et al.* (2010) reported that larger cerebellum hemispheres in men mirrors analogous observations in the cerebral cortex. In addition, similar trends in the anterior vermis replicate their findings in other samples. Similar sex differences in other cerebellar lobules. However, sexual dimorphism in the size of cerebellum hemispheres and the anterior vermis appears robust, whereas the differences in the posterior vermis are weaker and need to be replicated.

In addition, a study by (Rhyu *et al.*, 1999b), revealed that cerebellum volume of males was bigger than that of females (Table 1). However, Luft *et al.* (1997a) reported that there was no gender difference in cerebellar volume when the volume was corrected by intracranial volume. Interestingly the area of vermis of both sexes was not statistically different. This may suggest that the gender difference of cerebellar volume is mainly due to the difference of cerebellum hemisphere which needs to be further explored.

Table 2.1 Distribution of vermis area and cerebellar volume according to age and sex (Rhyu *et al.*, 1999b)

Age	Female			Male		
	Number	Vermis	Volume	Number	Vermis	Volume
20–29	11	12.5 ± 1.7	116.6 ± 10.3	9	11.2 ± 0.9	132.1 ± 6.8
30–39	9	11.5 ± 0.7	112.7 ± 10.7	10	10.0 ± 1.7	123.6 ± 10.9
40–49	13	11.7 ± 1.3	111.7 ± 12.8	10	11.9 ± 1.7	123.1 ± 10.3
50–59	10	12.0 ± 1.2	117.1 ± 6.1	10	11.6 ± 1.6	124.9 ± 9.7
60–69	12	10.2 ± 1.2	114.6 ± 7.2	11	11.9 ± 1.8	130.5 ± 11.0
70–79	12	10.3 ± 1.1	120.0 ± 13.8	7	9.6 ± 1.4	120.4 ± 11.7
Total	67	10.9 ± 1.4	115.4 ± 11.3	57	11.3 ± 1.6	126.0 ± 10.4

2.5 Clinical Significance of Cerebellar Volume

2.5.1 Schizophrenia

Recent studies indicate that the cerebellum is involved in schizophrenia. It is crucial for motor coordination and are associated with motor dysfunction in the disease. The concept of “cognitive dysmetria" hypothesizes a disruption in this cortico-cerebellar-thalamic-cortical circuit (CCTCC) leading to impaired sequencing and coordination of mental processes, manifested in symptoms associated with schizophrenia (Andreasen *et al.*, 1998). The important role of the cerebellum in motor coordination is well established. These functions are known to be deficient not only in patients with manifest schizophrenia, but also in probands with an increased genetic liability (Niethammer *et al.*, 2000).

A recent magnetic resonance (MR) imaging study reported an association between enlarged vermian white matter volume and positive symptoms in patients with schizophrenia (Levitt *et al.*, 1999). A longitudinal MR imaging study

of first-episode schizophrenia also reported volume reduction of the right cerebellum hemisphere (DeLisi *et al.*, 1997).

Coffman *et al.* (1990) found no differences between schizophrenics and controls, whereas Nasrallah *et al.* (1981) reported that schizophrenics have larger cerebellum structures than controls. However, a number of MRI studies could not confirm the vermal atrophy in schizophrenic patients. Two studies reported a greater rate of cerebellar atrophy in manic patients than in patients with schizophrenia or normal controls (Nasrallah *et al.*, 1981)

2.5.2 Autism and attention-deficit/hyperactivity disorder (ADHD)

Clinical, neuroanatomic, neurobehavioral, and functional brain-imaging studies suggest a role for the cerebellum in cognitive functions, including attention. The cerebellum has been implicated in several neurodevelopmental disorders such as attention deficit/hyperactivity disorder and autism (Bishop, 2002; Seidman *et al.*, 2005) and it may be particularly vulnerable to environmental insults (Lesnik *et al.*, 1998).

MR imaging evidence shows that cerebellum anatomical maldevelopment in autism is present before the end of the first year of life (Courchesne, 1997) and persists throughout subsequent development (Figure 2.6).

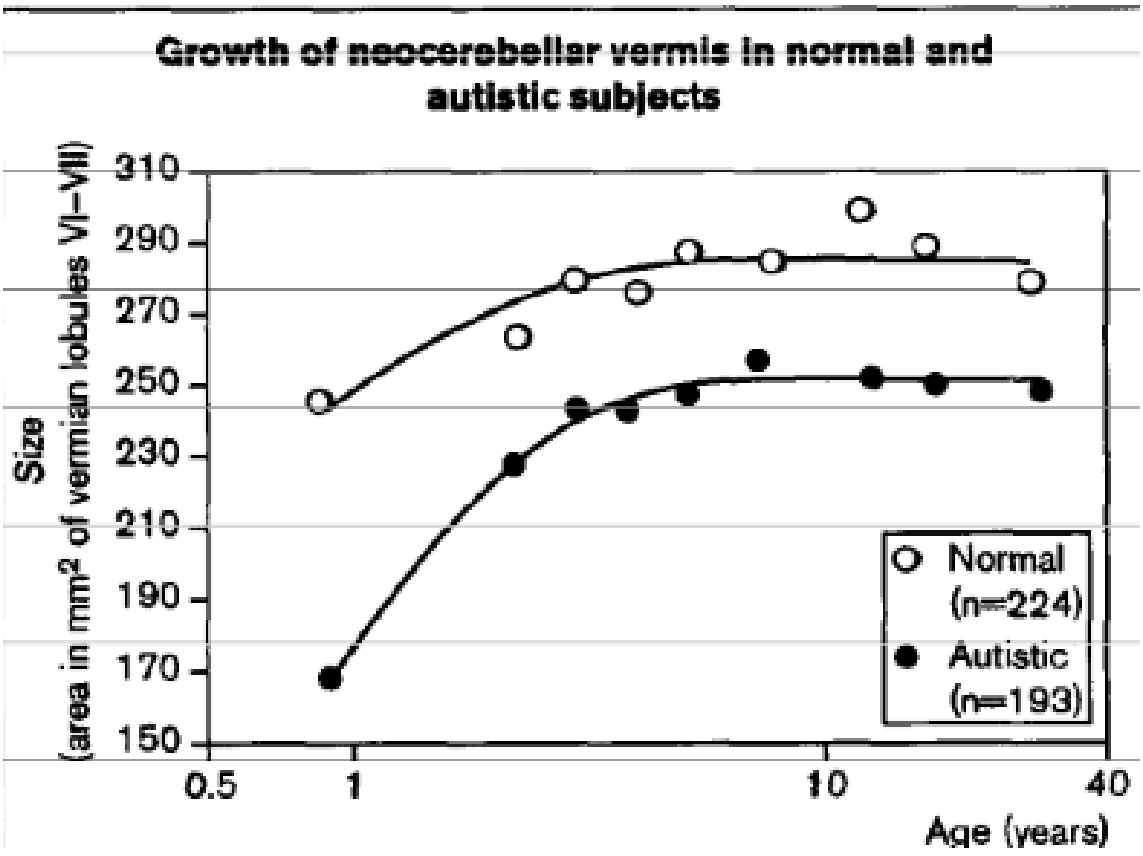

Figure 2.6 MR imaging results combined from many studies have shown that neocerebellar abnormality in autism is present by infancy and persists throughout subsequent development (Adapted from (Courchesne, 1997)

However, in study by Piven *et al.* (1992), they did not find significant differences between autistic subjects and controls in the mid-sagittal area of cerebellar lobules. They discover that important differences in the selection of controls and methods of analysis may account for differences between these results and those of other studies.

2.5.3 Bipolar Disorder

DelBello *et al.* (1999) reported, although historically the cerebellum was thought to only modulate movement, in fact, regions of the cerebellum are

closely interconnected with cerebral limbic areas, suggesting that the cerebellum may also modulate mood (Anand *et al.*, 1959; Courchesne *et al.*, 1989). Several case reports have identified cerebellar atrophy in patients with mood dysregulation and in patients with bipolar disorder (Cutting, 1976; Hamilton *et al.*, 1983; Yadalam *et al.*, 1985). Moreover, several studies have found abnormal cerebellum anatomy in patients with affective disorders (reviewed in Soares and Mann (1997).

Two studies reported a greater rate of cerebellar atrophy in manic patients than in patients with schizophrenia or normal controls (Nasrallah *et al.*, 1982). Additionally, Yates *et al.* (1987) found a greater rate of cerebellar atrophy in patients with bipolar disorder who were over fifty years old, but not in younger bipolar patients compared with healthy volunteers.

In another study by Strakowski *et al.* (2002), bipolar patients with multiple prior affective episodes exhibited a smaller vermal V3 area than healthy subjects. The vermal size was inversely correlated with the number of prior depressive episodes suggesting that the cerebellar vermis atrophy during the course of bipolar disorder.

2.5.4 Alzheimer's Disease

Alzheimer's disease (AD), is the most common cause of dementia beyond the age of 65 years. It's a degenerative brain disease clinically characterized by a variety of cognitive disturbances such as memory, language, and abstract thinking impairment. Neuropathological hallmarks of AD are the

appearance of neurofibrillary tangles and amyloid plaques in the brain parenchyma, accompanied by loss or degeneration of neuronal cells in distinct brain regions, particularly in the cerebellum (Thomann *et al.*, 2008). It is a region generally rather neglected in AD research, which also undergo degenerative changes (Braak *et al.*, 1989; Li *et al.*, 1994; Fukutani *et al.*, 1996; Baloyannis *et al.*, 2000; Sjöbeck and Englund, 2001; Wang *et al.*, 2002)and (Wegiel *et al.*, 1999). These alterations mainly comprise significantly reduced Purkinje cell density, atrophy of the molecular and granular cell layer as well as a large number of amyloid plaques in the cerebellar cortex of AD patients when compared to age-matched controls. The fact that atrophy was found to be significantly correlated with both clinical severity and duration of the disease suggests that cerebellar changes might be at least partly related to the basic pathologic process of AD (Wegiel *et al.*, 1999).

2.6 Volumetry Method

MRI-based cerebellum volumetric has been widely used in various neuropsychiatric disorders. In the past 20 years, the number of clinical studies using cerebellum volumetric assessment has increased rapidly because it is involved in various neuropsychiatric diseases, such as depression, schizophrenia, epilepsy, dementia, and sleep disorders.

To optimize the determination of cerebellum volume, various manual (Figure 2.7 by Rhyu *et al.* (1999a) and automated protocols have been described (Luft *et al.*, 1998). Despite the usefulness, manual methods of cerebellum isolation from magnetic resonance scans are laborious, subjective,

time consuming, and prone to operator errors. High-resolution 3D MRI data are now being employed routinely to quantify cerebellum anatomic volumes in normal and diseased subjects (Saeed and Puri, 2002).

A semi-automated technique addresses some of the drawbacks of manual segmentation, but the procedure described involves considerable preparation of the data for segmentation. Atlas-based methods are also available, and are designed for large population studies requiring segmentation of the cerebellum. These rely on manual segmentation of the cerebellum in the atlas followed by registration of the subject volume to the atlas using global and local transformation algorithms. The image registration procedures involved in such transformations are highly computer intensive (Dawant *et al.*, 1999).

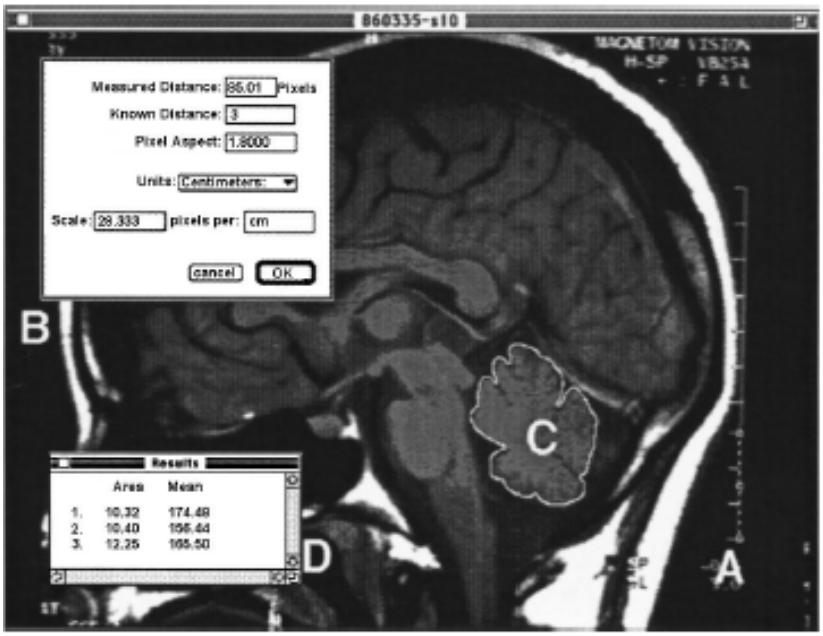

Figure 2.7 Captured screen of NIH image 1.60 for MRI analysis: Segmentation of midsagittal vermis and total cerebellum slice. Adapted from Rhyu *et al.* (1999b)

One key issue that must be addressed during the development of image segmentation algorithms is the accuracy of the results they produce. Algorithm developers require this so they can see where methods need to be improved and see how new developments compare with existing ones. Many metrics have been proposed to characterize error and success rates in segmentation, and several datasets have also been made public for evaluation. Still, the methodologies used in analyzing and reporting these results vary from study to study, so even when studies use the same metrics their numerical results may not necessarily be directly comparable (Shattuck *et al.*, 2008)

It has been validated both by comparing contours obtained manually and automatically and by repeating the measurements on serial acquisitions. Results demonstrate that the method is both robust and accurate, even in the presence of large morphological differences due to severe atrophy caused by chronic alcoholism (Hartmann *et al.*, 1999).

2.7 Normalization

Because volumes of subcortical structures and cerebellum depend on whole brain volume, it is necessary to control for brain size effects (Escalona *et al.*, 1991; Gur *et al.*, 1998; Sandok *et al.*, 2000). In a study by Szabo *et al.* (2003), they standardized the brain volumes by using spatial normalization, whereby 3D MR imaging datasets were reformatted to the dimensions of the Talairach brain. The method of spatial normalization implemented in the study standardized volumes of cerebral structures to total cerebral volumes in a

proportional manner, whereas the cerebellum volumes were adjusted passively but proportional to total cerebral volumes.

In study by Free *et al.* (1995), the intracranial area of a coronal section at the level of the anterior commissure was measured as an index of intracranial volume for normalization of the cerebellum volume data. In the study, the normalize cerebellum volume were in line with previous MRI structural studies of the cerebellum (Loeber *et al.*, 1999; Ichimiya *et al.*, 2001).

According to Free *et al.* (1995), normalization can be done most reliably by two standard methods, either by using by using ICV or CV as the correction factor. The normalization using ICV was done using covariance method as described by Jack et al. (1989).

Aylward *et al.* (1997) used methods where cerebellar volumes were divided by intracranial volume (ICV), yielding corrected volumes (ICV ratio). They compare subjects with Down syndrome and normal controls and suggested that for analysis of change in cerebellar volume with age, the intracranial volume (ICV) ratio is probably the most appropriate, as ICV provide index of how large the brain was before any atrophy occurred.

2.8 Estimating Intracranial Volume from MR Imaging

The cerebral volume is commonly used in various studies as a correction factor in volumetric studies. This is attributed to the fact that cerebral volume is faster and easier to be measured than ICV. However, implementing cerebral

volume as a normalizing factor may be inaccurate if the whole brain itself is already atrophic due to the effect of the neurological disorder.

ICV provides a more constant and precise normalization factor for estimating volumetric changes. Most of non-congenital neurological conditions do not affect the cranial size before it has completed its growth. Unfortunately, automated measurement of ICV is difficult from standard T1-weighted images due to poor contrast resolution between bone and underlying dura layer. Recognition of the dura mater is important in order to accurately measure the intracranial volume (Eritaia *et al.*, 2000a). Therefore the ICV measurement is preferably to be done by manual tracing, but it is laborious and time-consuming; a drawback for its wide clinical adaptation.

ICV measurements can be performed in various planes of MRI sequences. Linear interpolation of areas was used to obtain an estimate of ICV from segmented section. The number of slices and the slice thickness used to measure ICV are also varied significantly, and the definition of total ICV has been inconsistent across studies.